DETAILED ACTION

Election/Restrictions

Applicant's election of group I (claims 1-10 and 12) and election of hydroxy apatite wherein portion of hydroxyapatite substituted with Zn as the porous apatite, copolymer of polylactic acid and PEG as species of disappearing polymer and election of $ZnCl_2$ as the divalent metal salt in the reply filed on 3/14/08 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). The restriction is still deemed proper and made FINAL.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) or120 as follows: See MPEP 706.02(b) that states, "[T]he filing date of the priority document is not perfected unless applicant has filed a certified priority document in the application (and an English language translation, if the document is not in English)". Applicants are required to provide a English translation of the priority document.

Claims 1-12 are pending.

Claims 11 have been withdrawn from further consideration as being drawn to non-elected invention.

Claims 1-10 and 12 are examined on the merit.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10 and 12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is drawn to a protein drug sustained-release microparticle for injection, characterized by comprising a porous apatite or derivative, comprising a protein drug coated with or adhered to an in vivo disappearing polymer.

The claims are drawn to porous apatite of unknown composition comprising a protein drug and an in vivo disappearing polymer. Thus, the claims are genus claims. The specification and claims do not indicate what distinguishing attributes are shared by the members of the genus. Specifically, the specification does not clearly define a porous apatite or derivative, "a" protein drug, and an in vivo disappearing polymer. With the exception of hydroxy apatite-Zn porous apatite, the current specification does not disclose other porous apatite material. The claim 1 as recited also does not define the nature of the porous body in terms of its chemical composition and physical characteristics with regards to size of the particle and porous size. The mere mention of 'a protein drug' does not provide adequate written description to the instant application. Applicants have defined the "protein drug" as a protein having a molecular weight

>5000 d. Number of proteins that conform to this definition are innumerable. Applicants have disclosed only a few in their specification and used only IFN-alpha, insulin and hGH in their specific examples. Applicants are not in possession of all the genera of different classes of compound encompassed by the term "a protein drug". Like wise the limitation "in vivo disappearing polymer" is either defined in the claim 1 as recited, nor disclosed in the specification to support the instant invention commensurate with the scope. Thus, the scope of the claims includes numerous structural and functional variants, and the genera are highly variant because a significant number of structural and functional differences between genus members is permitted. The specification and claims do not provide any guidance as to what changes should be made. Structural and functional features that could distinguish a porous apatite derivative, a human growth hormone, and a water-soluble divalent metal compound are missing from the disclosure. No common attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, a porous apatite derivative, a human growth hormone, and a water-soluble divalent metal compound are insufficient to describe the genus.

The MPEP clearly states that the purpose of the written description is to ensure that the inventor had possession of invention as of the filing date of the application, of the subject matter later claimed by him. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Lockwood v.

American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir.1997). The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the application. These include, "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed invention is sufficient" MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated: "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

The written description requirement for a claimed genus' may be satisfied through sufficient description of a representative number of species by actual reduction to practice,

reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the genus for a porous apatite or derivative, a protein drug, and an in vivo disappearing polymer.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostelli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In re Gostelli, 872 F.2d at 1012, 10 USPQ2d at 1618.

The claim(s) 1-10 and 12 contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-5 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims 2, 4, 5 and 12 recites a limitation, "block copolymer consisting of polyethylene glycol and polylactic acid or copolylactic-glycolic acid" It is unclear from the claim as recited as defining the two copolymers as 1) polyethylene glycol and polylactic acid and 2) copolylactic-glycolic acid; or copolymers as 1) polyethylene glycol and polylactic acid or 2) polyethylene glycol and copolylactic-glycolic acid.

The claim 3 recites a limitation, "block copolymer consisting of polyethylene glycol and polylactic acid or copolylactic-glycolic acid is a block copolymer consisting of polylactic acid or copolylactic-glycolic acid-polyethylene glycol-polylactic acid or copolylactic- glycolic-acid". It is unclear from the claim as recited the nature and composition of copolymers claimed in the instant claim. It is difficult envision the exact nature in terms of chemical composition of the copolymer composition from the claim as recited, because, it is unclear which polymer is copolymerized which other polymer recited in the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 6-8 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by JP 2001-158429 of Yutaka, et al.

In the instant invention applicants claim a protein drug sustained-release microparticle for injection, characterized by comprising a porous apatite or derivative, comprising a protein drug coated with or adhered to an in vivo disappearing polymer.

The reference of Yutaka discloses a sustained release microparticle drug composition of medicinal proteins wherein the microparticle comprises of inorganic material (abstract). The inorganic material of the cited reference is calcium phosphate (disclosed in claim 6 of the cited reference), the protein drug could be hGH the instant elected species (disclosed in claim 4 of the cited reference), the polymer disclosed is the lactic acid-glycolic acid polymer which is a co-polymer of two species (disclosed in claim 10 of the cited reference), and the cited reference also discloses that composition is for subcutaneous or intramuscular injection. Hence meets the limitations of instant claims 1-3. The cited reference also discloses that the percentage of biologically active substance is in the range 0.0001 to 10% (disclosed in claim 3 of the cited reference), and hence reads on instant claim 7. The diameter of the microparticle disclosed in the cited reference is in the range 10-1000 nm (disclosed in claim 8 of the cited reference), and hence reads on the instant claim 8. The example 8 (page 8, [0034]) of the cited reference

discloses that solution of zinc acetate was used in the composition. The presence of Zinc ions in the composition illustrates the fact Zn ions replaces the calcium in the inorganic microparticle and hence reads on the instant claim 10.

Therefore, the cited reference of Yutaka anticipates the instant invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 6, 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 2001-158429 of Yutaka, et al., as applied to claims 1-3, 6-8 and 10 above, and further in view of US 2002/0076447 of Ito.

In the instant invention applicants claim a protein drug sustained-release microparticle for injection, characterized by comprising a porous apatite or derivative, comprising a protein drug coated with or adhered to an in vivo disappearing polymer.

The reference of Yutaka discloses a sustained release microparticle drug composition of medicinal proteins wherein the microparticle comprises of inorganic material (abstract). The inorganic material of the cited reference is calcium phosphate (disclosed in claim 6 of the cited reference), the protein drug could be hGH the instant elected species (disclosed in claim 4 of the cited reference), the polymer disclosed is the lactic acid-glycolic acid polymer which is a co-polymer of two species (disclosed in claim 10 of the cited reference), and the cited reference also discloses that composition is for subcutaneous or intramuscular injection. Hence meets the limitations of instant claims 1-3. The cited reference also discloses that the percentage of biologically active substance is in the range 0.0001 to 10% (disclosed in claim 3 of the cited reference), and hence reads on instant claim 7. The diameter of the microparticle disclosed in the cited reference is in the range 10-1000 nm (disclosed in claim 8 of the cited reference), and hence reads on the instant claim 8. The example 8 (page 8, [0034]) of the cited reference discloses that solution of zinc acetate was used in the composition. The presence of Zinc ions in the composition illustrates the fact Zn ions replaces the calcium in the inorganic microparticle and hence reads on the instant claim 10.

The reference of Yutaka does not teach the elected species of hydroxyapatite in which a portion of the calcium is substituted with Zinc and that the porous apatite is treated in the range from 100-600 ^{0}C.

The reference of Ito discloses hydroxyapatite (calcium phosphate) that contains Zn atoms in the form of a microparticle for treating Zn deficiency (abstract). The reference teaches that sparingly soluble zinc containing calcium phosphate can be obtained by heating a soluble zinc containing calcium phosphate at 200 ^{0}C [0046]. The cited reference of Ito also discloses $CaZn_2(PO_4)_2$ nH2O($1 \leq n \leq 2$) corresponding to the elected species $Ca_{10-x}Zn_x(PO_4)_6$ $(OH)_2$($1 \leq n \leq 2$) in the absence of a value of x in the formula. Since the temperature used in the aforementioned process of preparing sparingly soluble zinc containing hydroxyapatite is within in the temperature range recited in the instant claim 9, the disclosure of Ito reads on the instant claim 9. In the aforementioned process the zinc ion replaces the portion of the calcium in the porous apatite of calcium phosphate and hence meets the limitations of instant claim 10. Ito also discloses polyethyleneglycol in the composition [0140] one of the elected species.

It would have been obvious to one of ordinary skill in the art to modify the teachings of Yutaka and Ito to arrive at the instant invention. One would have been motivated to do so given the fact that calcium phosphate microparticles could be used in the preparation of an injectable composition for protein drugs comprising in vivo disappearing polymers as shown by Yutaka and the hydroxy apatite microparticles can be prepared as shown by Ito. One skilled in the art would have had reasonable expectation success given the fact the calcium phosphate of Yutaka and modified microparticle of Ito with zinc atoms replacing the calcium atoms in the matrix has been successfully used in the preparation of composition for injections.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the

forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-10 and 12 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 7,378,394 B2 issued to Ogawa in view of JP 2001-158429 of Yutaka, et al.

In the instant invention applicants claim a protein drug sustained-release microparticle for injection, characterized by comprising a porous apatite or derivative, comprising a protein drug coated with or adhered to an in vivo disappearing polymer.

In the U.S. Patent No. 7,378,394 B2 claims 1-4 are drawn to human growth hormone sustained-release microparticle, characterized by comprising a zinc containing porous hydroxyapatite.

The cited U.S. Patent No. 7,378,394 B2 does not teach the use of in vivo disappearing polymer in the composition.

The reference of Yutaka discloses the use of copolymers of lactic acid-glycolic acid polymer (disclosed in claim 10 of the cited reference), and the cited reference also discloses that composition is for subcutaneous or intramuscular injection.

It would have been obvious to one skilled in the art combine the teachings of the U.S. Patent No. 7,378,394 B2 and the teachings of Yutaka to arrive at the instant invention. One would have been motivated to do so given the fact Yutaka teaches the aspects of use of copolymers of lactic acid and glycolic acid. One would have had reasonable expectation of success given the fact use polymers in compositions comprising calcium phosphate and protein was successfully demonstrated by Yutaka.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the

references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyanarayana R. Gudibande whose telephone number is 571-272-8146. The examiner can normally be reached on M-F 8-4.30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Satyanarayana R Gudibande/
Examiner, Art Unit 1654

/Andrew D Kosar/
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